REMARKS/ARGUMENTS

STATUS OF CLAIMS

Claims 2-69 are cancelled. Claims 1 and 70-109 are pending. Claims 1, 78, 84, 92, 96, 100-101, and 106-107 are amended above.

THE AMENDMENTS

The Office Action indicated that the subject matter of claims 84, 92, 100-101, and 106-107 was allowable if rewritten in independent format. Claims 92 and 107 have been rewritten in independent format. Claims 84, 100-101, and 106 have been amended to depend from these newly independent claims. Thus it is respectfully submitted that these claims are in condition for allowance. In addition, it is also submitted that claims 78-79, 98, and 104 which depend from allowable claim 92 are also in condition for allowance.

All remaining claims have been amended so that they ultimately depend from claim 96. Claim 96 recites that the exogenous nucleic acid is administered by perfusion through vasculature of the tissue of interest. Many previously presented claims recited administration by perfusion. See, for example, claims 78, 79, 99, 104, 105. The specification teaches administration of exogenous nucleic acid by perfusion through vasculature of the tissue of interest *inter alia* at page 65, lines 6-11, page 65, line 30 to page 66, line 7, page 66, lines 17-22, page 69, lines 14-20, and page 70 in its entirety. In addition, Example 1 employed perfusion as the method of delivery of the exogenous nucleic acid. Thus the amendment of claim 96 is fully supported in the specification and does not add new matter.

The Rejection of Claims 1, 70-83, 85-91, 93-99, 102-106, and 108-111 Under 35 U.S.C. § 112, first paragraph

Claims 1, 70-83, 85-91, 93-99, 102-106, and 108-111 stand rejected as not enabled for their full scope. These claims are allegedly enabled only for *ex vivo* delivery of nucleic acids and direct injection of nucleic acids, but not for all *in vivo* methods of delivery. This rejection is respectfully traversed.

Claims 1, 70-83, 85-91, 93-99, 102-106, and 108-111 have been amended to recite that "the exogenous nucleic acid is administered by perfusion through vasculature of the tissue of interest."[1] It is respectfully submitted that the specification enables the full scope of the claims as amended.

The Office Action cites three literature references: Anderson (*Nature*, 1998), Verma (*Nature*, 1997), and Palu (*J. Biotech*, 1999). These references are cited to demonstrate that gene transfer and expression in humans is inefficient (Anderson), and that long-term expression is difficult to achieve (Verma and Palu). However, none of these references mentions or considers the gene delivery method of the claimed methods; none discusses the use of perfusion through vasculature of a tissue interest. Thus, the direct relevance of these references to the claimed methods is minimal.

Anderson divides gene therapy into three categories: *ex vivo*, *in situ*, and *in vivo*. The Patent and Trademark Office has already indicated that the subject application enables the invention with regard to the first two categories, *i.e.*, *ex vivo* and direct injection to a tissue (*in situ*). Only the third category, *in vivo*, is questioned by the Patent and Trademark Office. However, since none of the references even considers the type of *in vivo* delivery claimed, *i.e.*, perfusion, they can not bear on the question of enablement of *in vivo* perfusion.

Moreover, applicants provide with this amendment evidence which shows the successful use of *in vivo* perfusion as a means of delivering nucleic acids to tissues. The enclosed declaration of Dr. Kevin Donahue along with the attached publications from *Nature Medicine* and *Circulation* demonstrate the successful use of *in vivo* perfusion to deliver nucleic acids to a desired tissue. One of the publications reports that gene transfer by means of *in vivo* perfusion resulted in a reduction in ventricular rate during atrial fibrillation. See Exhibit I and paragraph 3 of the declaration. The other publication reports physiologically relevant heart rate control in persistent atrial fibrillation after *in*

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[1] Claim 96 was actually amended and the remaining claims now depend directly or indirectly on claim 96.

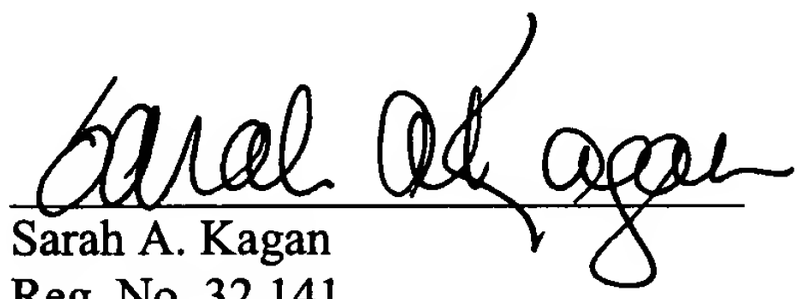
vivo perfusion to the atrioventricular nodal artery. See Exhibit II and paragraph 4 of the declaration. This evidence of success using the claimed perfusion method is more pertinent than general references which do not even consider perfusion.

It is respectfully submitted that the full scope of the claims as amended is enabled by the specification as filed.

Withdrawal of this rejection is therefore appropriate.

Respectfully submitted,

Dated: January 5, 2005

By: 

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